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Effects of Positive End Expiratory Pressure and Counterpressurization on Circulating Prostaglandins in the Dog

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The effects of the application of positive end expiratory pressure (PEEP) ventilation, with and without body counterpressure (CP), on circulating prostaglandin-like substances (PGL) were studied in chloralose anesthetized dogs. The normal respiratory movements were paralyzed with succinylcholine chloride. Arterial levels of PGL were continuously bioassayed using Vane's blood superfusion method. PEEPs of 10 and 20 mm Hg elicited PEEP-related increases in functional residual capacity and circulating PGL levels and decreases in blood pressure, left ventricular dP/dt, and heart rate. The PGL appeared to be PGE or prostacyclin in character. When PEEP and CP were simultaneously applied, the increments or decrements of indices described above were reduced. It is concluded that increases in the levels of circulating PGL are attributable, at least in part, to hyperexpansion of the lungs during PEEP and that some of the cardiovascular deterioration observed during and after PEEP may be the result of the vasodilating and cardiodepressing effects of PGL.

VENTILATION WITH positive end expiratory pressure (PEEP) is used not only in supporting patients with an insufficiency of the cardiorespiratory system but also in aviation medicine where, in the event of cabin pressure loss during high-altitude flights over 12,000 m, adequate arterial oxygen tension must be maintained. It has been shown, in both conscious, actively respiring human subjects and anesthetized, artificially ventilated animals that prolonged exposure to PEEP elicits deterioration of the cardiovascular system (4,5,6,8,11,17,20).

Among the many explanations for this cardiovascular deterioration has been the role of humoral factors. Piper and Vane (15) noted the release of prostaglandin-like substances (PGL) during PEEP and attributed this release, at least in part, to hyperinflation of the lung. The release of cardiodepressor substances and PGL during PEEP have also been reported (3,7,9,10,12,18,21).

In this report, we wish to examine both the alterations in circulating PGL levels during PEEP in artificially ventilated anesthetized dogs whose respiration was paralyzed with succinylcholine and whether the application of counterpressure to the thorax and extremities affects these changes.

MATERIALS AND METHODS

Mongrel dogs of either sex weighing 16–20 kg were anesthetized with 1% alpha-chloralose (100 $mg \cdot kg^{-1}$ i.v.) (B.D.H.). Anesthesia was maintained with a constant infusion of chloralose at the rate of 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ i.v. Succinylcholine chloride (0.2 $mg \cdot min^{-1}$) (Sigma) and a mixture of sodium bicarbonate (16.8 $mg \cdot ml^{-1}$) (Fisher) and dextrose (60 $mg \cdot ml^{-1}$) (Fisher) were continuously infused intravenously. All solutions were constituted in 0.9% saline and the total combined volume·min^{-1} of infusates was 1.0 $ml \cdot min^{-1}$.

Arterial blood pressure (P_a) was recorded from a cannula placed in the right brachial artery. A left ventricular catheter was inserted retrogradely via the left carotid artery. The point of insertion of the left ventricular catheter was 3–4 cm proximal to the bifurcation of the inominate artery and 2–3 cm distal to the carotid sinus. The dP/dt (left P_{vt} dP/dt) signal derived from the left P_{vt} was used to trigger a cardiotachometer (Grass 7P4)

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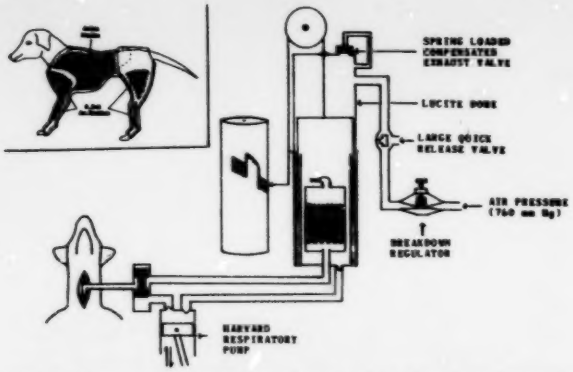

Fig. 1. Apparatus for the positive end expiratory pressure breathing studies in the anesthetized dog. The Benedict Roth type spirometer was modified as described in the text. *Inset:* Counterpressurization assembly for the dog consisted of a jerkin and G suit for thorax and extremities counterpressure. Abdominal area was not counterpressurized. The jerkin and legging contained air bladders sandwiched between two layers of nylon fabric at appropriate anatomical areas. Velcro (for the jerkin) and zipper (for the G suit) fasteners were used for close fitting.

which recorded heart rate (HR). Tracheal pressure and end-expiratory CO_2 samples were measured with the Beckman LB2 CO_2 analyzer from side arms of a tracheal tube inserted proximal to the larynx. All pressures were measured with Statham P23 Dc pressure transducers and were recorded on the Grass Model 7 polygraph. Body temperature was maintained at 37.5 ± 0.5°C by means of an electrical heating pad controlled with an esophageal thermistor probe placed at the level of the heart and a temperature control unit (Yellowsprings Instruments 73A).

On completion of surgical procedures, the dog was fitted into a counterpressure assembly which consisted of a Jerkin for thorax counterpressure and G suit for extremities counterpressure (Fig. 1). The assembly was fabricated by the Medical Life Support Division of the Defence and Civil Institute of Environmental Medicine, Downsview, Ont., Canada. The apparatus used for PEEP studies consisted of a Harvard small animal respirator connected to a Benedict Roth-type spirometer. The latter was modified with an air-tight Lucite dome over the floating bell (Fig. 1) so that the required pressure for the induction of PEEP could be applied to the bell. A spring-loaded compensating exhaust valve attached to the Lucite dome prevented airway pressure from exceeding 8–10 mm Hg above PEEP. The pressure was applied from a compressed air source by use of a 7-in diameter propane breakdown regulator. The airway pressure was adjustable from 1–100 mm Hg. During application of PEEP, the animal was respired with 100% O_2, but was changed to room air during resting periods between each PEEP event. A control period of respiration with O_2 was commenced 15 min prior to the application of PEEP. Thus, during resting periods between events and during control periods before PEEP, the animal was respirated with room air by intermittent positive pressure ventilation (IPPV). The alteration in function residual capacity (ΔLV) elicited by PEEP was estimated by measuring the shift of the baseline recorded on the spirometer chart, and then adjusting the recorded volume increase for compression of the gases according to Boyle's Law. The average changes in functional residual capacity with PEEPs of 10 and 20 mm Hg were 733 ml and 1073 ml, respectively.

Bioassay: A blood superfusion cascade method described by Moncada *et al.* (13) was used to identify and quantify the circulating autacoids. Tissues used were rat stomach strips (RSS) obtained from the fundus portion of the stomach, longitudinal strips from the ascending rat colon (aRC), and longitudinal strips of chick rectum (CR) 3 d–3 weeks old. The tensions developed by each of the three tissues were measured using Grass FT03C Force displacement transducers, and the Grass Model 7 recorder. The tensions of the tissues were kept as isotonic as possible by the use of a soft spring between the tissue and the transducer. The following modifications were made to the method of Moncada *et al.* (13): tissues were initially superfused continuously at 3 $ml \cdot min^{-1}$ for a minimum of 30 min with Tyrode's solution containing the following antagonists in $g \cdot ml^{-1}$—mepyramine maleate (Sigma) 1×10^{-5}, propranolol HCL (Ayerst Labs) 2×10^{-6}, atropine methyl bromide 1×10^{-7} (Sigma), phentolamine HCL 2×10^{-7} (CIBA), and methysergide 2×10^{-7} (Sandoz). The solution was adjusted to pH 7 with NaOH; then indomethacin 1×10^{-6} (Merck Sharp and Dohme) was added. This perfusion allowed time for the tissues to be antagonized against their respective agonists. At least 90% blockade was obtained at concentrations of agonist which gave submaximal contraction. The superfusion system was then switched over to an extracorporeal blood superfusion system from the femoral artery at the rate of 3 $ml \cdot min^{-1}$. The drained blood was pumped back into the right atrium. The tissues were allowed to stabilize in blood for 5–10 min before PEEP studies commenced. The activity of the tissues was continuously monitored until a baseline level was reached 10–20 min after the release of PEEP. It was previously experimentally established that pharmacological blockade was effectively maintained in the tissues for at least 30 min of blood superfusion. The tissues were then taken off blood and switched back to superfusion with the Tyrode's/antagonists solution for at least another 30 min so that 45–60 min lapsed between PEEP intervals. This modification of procedure permitted us to maintain specific pharmacological blockade of the bioassay tissue without significant quantities of the antagonist entering into the dog circulation. In the arterial circuit, there was a transit time delay of 30–35 s for substances to travel from the femoral artery to the tissues.

In order to calibrate the assay system, several concentrations of PGE_2 (Upjohn Co.) were infused into the Tyrode's superfusate until steady states of contraction of the assay tissues were obtained. The increments in circulating PGL levels were calculated from the maximal responses of the respective tissues and expressed as nanograms of PGE_2 equivalents.

The RSS was used for quantifying PGL levels; aRC CR were used for identification. In order to meet criteria for the presence of prostaglandin-like substances (PGL) it was necessary to obtain contractions of all three tissues.

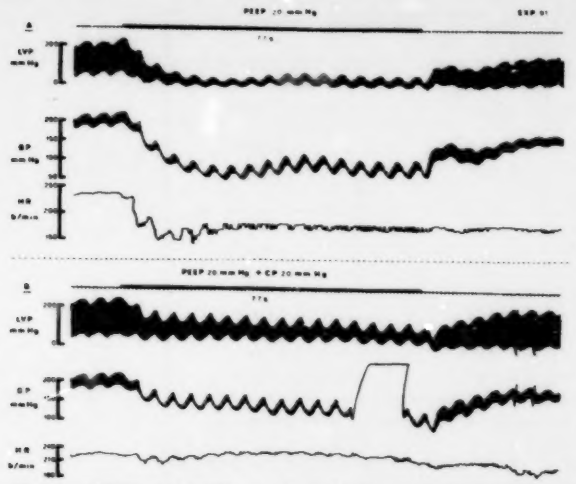

Fig. 2. Effects of positive end expiratory pressure with and without counterpressure. (A) the effect of 20 mm Hg positive end-expiratory pressure (PEEP) (depicted by solid line) on the left ventricular pressure (LVP), systemic arterial blood pressure (BP) and heart rate (HR). (B) effects of 20 mm Hg PEEP with simultaneous application of 20 mm Hg counterpressure on the thorax and extremities.

RESULTS

In our protocol, we exposed our animals to 75 s of PEEP. It was felt that, during this period, all major immediate cardiovascular adjustments would have occurred and could be considered in our analysis. It also prevented serious deterioration of the preparation in high PEEP exposures.

The effects of application of PEEP are shown in a representative experiment (Fig. 2). It can be seen that PEEP of 20 mm Hg caused precipitous decreases in BP, left Pvt, and HR which persisted during PEEP exposure. The release of PEEP resulted in recovery of HR and LVP within approximately 10 s. BP usually took longer to reach pre-PEEP levels, the mean recovery period to 90% of control levels after termination of PEEP of greater than 15 mm Hg was 68.0 ± 10 s. The effects of PEEP of 10 mm Hg and 20 mm Hg are summarized in Table I. There were PEEP-related increases in functional residual capacity (ΔLV) and PEEP-related decreases in BP and LVP dP/dt. The mean HR responses were widespread because of interdog variability. In some animals at PEEP of greater than 15 mm Hg, the initial bradycardia was followed by reflex increases in HR, BP, and dP/dt; in other animals, as seen in Fig. 2, both bradycardia and hypotension persisted.

When counterpressure and PEEP were applied simultaneously at 20 mm Hg, maximum pressure was reached within 3–4 s. The decrements in BP, left Pvt, and HR seen with PEEP-only were markedly reduced (Fig. 2b). In other experiments, there were transient decreases in BP, left Pvt, dP/dt, and HR followed by compensatory responses. Table I tabulates the changes in cardiorespiratory indices during PEEP of 10 and 20 mm Hg with and without counterpressure. Although application of counterpressure markedly reduced the extent of lung expansion, the magnitude of hypotension and the negative inotropic responses, they never attained pre-PEEP levels.

Superfusion Studies: There was a concentration-related contraction of the treated rat stomach strip (RSS), ascending rat colon (aRC), and chick rectum (CR) to standard infusions of PGE_2. The threshold for detection of PGE_2 was 0.1–0.2 $ng \cdot ml^{-1} \cdot min^{-1}$.

Application of PEEP elicited biphasic responses in the naive RSS; in the treated RSS only contractile response was observed and this was attributed to PGL. The initial relaxation in the naive RSS tended to obscure the secondary PGL contraction. This relaxation was attributed to catecholamines because it was absent in tissues pretreated with adrenoceptor blockers.

In order to specifically identify PGL activity and rule out other endogenously released smooth muscle stimulating substances, chick rectum (CR) was substituted for the naive RSS in the assay.

The tracings in Fig. 3A show contractions in the three tissues elicited by endogenously released PGL as the result of application of PEEP. They were obtained during the same PEEP event as shown in Fig. 2A, but were recorded at a slower paper speed and thus cover a longer time period. There was a 60–90 s delay from the time of PEEP to the assay tissues reaction due, in part, to blood transit time to the various tissues and to the slow responses of the smooth muscle preparations. In this experiment, application of 20 mm Hg elicited maximum contractions equivalent to approximately 1.5 $ng \cdot ml^{-1}$ of PGE_2.

In 12 experiments, 6 show PEEP-related increases in PGL concentrations in the arterial blood (Fig. 4). In 2, only one PEEP level was used and positive PGL responses were detected. In the remaining 4 experiments, changes in circulating PGL levels were below 0.2 ng/ml or tissue responses were too erratic and unreliable.

Simultaneous application of counterpressure and PEEP resulted in decreases in PGL levels (Fig. 3B). This is the same PEEP event as shown in Fig. 2B. The PGL levels during this episode was approximately 0.3 ng PGE_2 equivalents (note differences in sensitivity settings). In Fig. 5, results of five PEEP episodes with counterpressurization are shown. Readings at 0.1 ng PGE equivalents represent subthreshold values.

DISCUSSION

There are of course many differences between the present study and conscious human studies in which inspiration is passive and expiration is forced. In anesthetized animal studies and human subjects undergoing assisted respiration, the inspiration is forced and expiration is passive.

The consequence of PEEP is one of cardiovascular depression. Even when counterpressurization is applied, cardiovascular impairment has been described in man (1,5,8). The failure to maintain cardiac output has been attributed to right ventricular failure because of pulmonary vascular compression (17), dysfunction of the left ventricle, or impeded venous return (16). Neural factors have also been implicated (6,19). It has been suggested that humoral factors may also play an important role in the physiological responses to PEEP (3,9,12,18). Our experimental model was designed so

TABLE I. EFFECTS OF POSITIVE END EXPIRATORY PRESSURE AND COUNTERPRESSURE EQUAL TO PEEP.

	PEEP mm Hg	No Counterpressure*	With Counterpressure*
Δ Function residual capacity (ΔLV in ml/kg)	10–14	40.2 ± 2.4 (16)[a]	20.5 ± 2.2 (15)[ab]
	20–22	78.1 ± 2.8 (12)[a]	36.2 ± 4.9 (10)[ab]
Δ Arterial B.P. (mm Hg)	10–14	−16.8 ± 3.5 (15)[a]	−4.1 ± 2.4 (15)[b]
	20–22	−57.2 ± 6.5 (12)[a]	−21.8 ± 7.1 (10)[ab]
Δ Heart Rate (b/min)	10–14	11.2 ± 9.1 (16)	30.4 ± 4.8 (15)[a]
	20–22	7.9 ± 7.1 (12)	17.6 ± 7.1 (10)[a]
Δ LVP dP/dt (% change)	10–14	−23.0 ± 6.8 (5)[a]	9.2 ± 3.6 (4)[a]
	20–22	−52.6 ± 5.8 (5)[a]	53.8 ± 11.5 (4)[a]

* Values represent mean ± standard error of the mean; number of experiments in parentheses.
[a] at $p<0.05$, values are significantly different from control.
[b] at $p<0.05$, values for counterpressure are significantly different from values with no counterpressure.

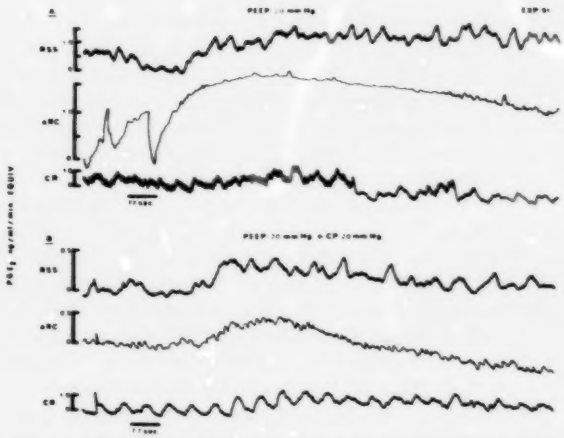

Fig. 3. Responses of blood superfusion cascade tissues to PEEP episodes with (B) and without (A) counterpressure. Tracings represent the same PEEP episodes as in Fig. 2. Note slower paper speed. Strips of rat stomach fundus strips (RSS), ascending rat colon strip (aRC), and chick rectum (CR) were superperfused with blood from the femoral artery. Changes in developed tension are calibrated in terms of tension changes due to known infusion of PGE_2 and expressed in ng·ml^{-1} (PGE_2 equivalents).

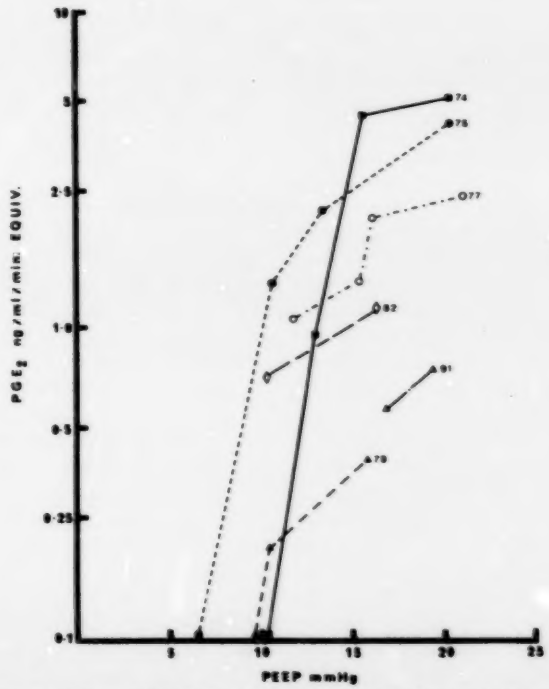

Fig. 4. Effects of PEEP on circulating prostaglandin-like substance (PGL). The numbers on each line are experiment designation numbers.

that the cardiorespiratory events and changes in circulating substances could be studied simultaneously.

Application of PEEP elicited decreased cardiac output, negative inotropic effects, hypotension, and bradycardia. The appropriate counterpressurization placed on body regions most susceptible to increased tracheal pressure, such as the thorax and the extremities, where venous engorgement occurs, alleviated cardiovascular impairment due to PEEP.

At PEEP levels greater than 20 mm Hg, cardiovascular impairment was still evident, although reduced, during the application of counterpressure. It suggests, therefore, that either there is an increased afterload, and thereby a decrease in heart function (decreased dP/dt), and/or an increase in circulating cardiodepressor substances during counterpressure. The observation of prolonged recovery times of the BP after release of PEEP indicated that slow-acting humoral factors may be involved.

In our hands, the *in vivo* estimation of PGL levels was difficult, principally because of the unstable nature and relative insensitivity of the bioassay system. In most preparations, contracting and relaxing substances were detected after PEEP. According to the criteria set forth by Moncada *et al.* (13), the principal autacoids were PGL, catecholamines, and angiotensin. It would be expected that catecholamines and angiotensin would be detected because of sympathetic reflex responses to the hypotension elicited by PEEP. However, despite the

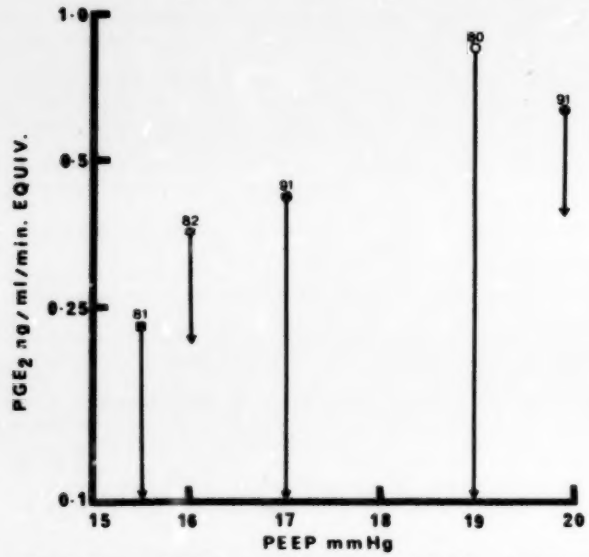

Fig. 5. Effects of PEEP on circulating PGL with (▼) and without (●,○,■,◆) counterpressurization.

relaxations due to catecholamine release, contractions of the tissues were still observed indicating the presence of PGL. Treatment of the tissues with antagonists resulted in unmasking the full contractile responses of the tissues, thus demonstrating the presence of PGL. We did not attempt to identify or quantify other autacoids at this time. The PGL concentrations reached were in the range of 0.5–5.0 ng/ml. Considering the nonspecific nature of the PGL measurement, these levels appear to be reasonable.

In a preliminary study, we reported PEEP-dependent decreases in aortic blood flows at the diaphragm level (21). In the present study, simultaneous cardiac output was not taken. We therefore cannot be certain that there were net changes in PGL output or whether the increased PGL level merely reflected decreased blood flow. Nevertheless, blood concentrations of PGL levels were elevated and thus may play a role in cardiovascular depression during and after PEEP. PGL has been shown to be released by several mechanisms. In addition to lung expansion, it is known that norepinephrine, epinephrine, and serotonin stimulate PG biosynthesis in the pulmonary system (14). Also reported is interrelationship between levels of activation of the renin-angiotensin system and circulating prostacyclin levels (22).

Changes in levels of circulating PGL due to PEEP have been observed to be effective in causing cardiovascular deterioration. This has been demonstrated in studies where PG synthesis was inhibited with indomethacin under experimental conditions similar to the present studies (unpublished data). It confirms reports that PG synthetase inhibitors improve the cardiovascular status of animals subjected to PEEP (3,9,12,18). On the other hand, Herbaczynska-Cedra *et al.* (10) state that PEEP-induced PGL increases are not prevented by aspirin-like substances.

The role of PGL in PEEP is not limited to the cardiovascular system. It has also been reported that pretreatment of dogs with indomethacin caused significant reduction in the functional residual capacity at various PEEP levels (2). This suggests that endogenous bronchodilator PGL is released during PEEP which, in turn, would dilate the peripheral bronchial tree and the pulmonary vasculature.

The application of counterpressure with PEEP reduced the blood levels of PGL. Again, we cannot be sure that this reduction is due to prevention of lung expansion or because of the improved cardiovascular status. It was interesting to note that, in several dogs, application of counterpressure only slightly reduced the PGL level rise. More recent studies in artificially ventilated anesthetized dogs show that even though systemic BP is maintained during PEEP plus counterpressure, there were still significant decrements in cardiac output and left Pvt dP/dt (unpublished data). It suggests that cardiodepressor substances similar to that described by Grindlinger and collaborators (7,9,12) are still being released in spite of the counterpressurization. This may explain why cardiovascular deteriorations are encountered in human studies in which simultaneous PEEP and counterpressure are applied (1,8).

In summary, these studies show that application of PEEP dependent decreases in many cardiovascular indices and increases in the concentration of circulating PGLs which are PGE and/or PGI in character. Prevention of lung expansion and peripheral vascular pooling, by the application of counterpressurization, reduced the cardiovascular deterioration and also reduced the level of PGL increase elicted by PEEP.

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